

APPENDIX E. Developmental Neurotoxicity Data Waiver



Department of Pesticide Regulation



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MEMORANDUM

Arnold Schwarzenegger
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TO: Gary Patterson
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FROM: Joyce Gee *[original signed by Joyce Gee]*
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DATE: July 30, 2004

SUBJECT: Sulfuryl fluoride Rat Developmental Neurotoxicity Study: Waiver request by Dow for ProFume®

50223-072, DPR record 210020, contains a report from the United States Environmental Protection Agency (US EPA), Hazard Identification Assessment Review Committee (HIARC), dated October 31, 2003, TXR No.: 0052208, regarding sulfuryl fluoride. The author was Jessica Kidwell, addressed to Ed Budd and Michael Doherty, both of the US EPA, Health Effects Division. According to the report, meetings of the HIARC were held on two occasions, April 11, 2001, and October 31, 2003, with the latter recommendations superceding the earlier one, dated May 22, 2001.

The major topic for reconsideration was in regard to the Food Quality Protection Act (FQPA) and potential increased sensitivity of infants and children. In brief, the HIARC concluded that there is concern for neurotoxicity from exposure to sulfuryl fluoride, based on the acute, subchronic and chronic neurotoxicity studies in rats and the developmental studies in rats and rabbits, all using inhalation, and all of which the Agency found acceptable. There is also an acceptable 2-generation reproduction study by inhalation in the rat with no specific evidence of sensitivity of offspring. The conclusion of US EPA from these studies was one of no concern for pre- and/or post-natal toxicity of exposure to sulfuryl fluoride. Based, however, on the evidence of neurotoxicity (clinical signs, histopathology and disturbances in electrophysiological waveforms), the HIARC recommended a developmental neurotoxicity study in rats be required. In the absence of such a study, a 10X uncertainty factor would be used. Page 28 identifies two data gaps, a metabolism/pharmacokinetics study in rats (waived in 1993) and an inhalation developmental neurotoxicity study in rats.

The document also contains evaluation of other studies and the safety factors for various lengths of exposure. These comments, however, are not pertinent to this memorandum.

Federal Register 69 (15): 3253 (January 23, 2004) Rules and Regulations: According to this notice, the Agency was still requiring a developmental neurotoxicity study as of 1/3/04 as a condition of registration of ProFume for food use. The 10X uncertainty factor was still in place, based on the lack of this study. The Agency considered it possible that the NOEL from other



studies could become an effect level. Based on the data available, EPA had no justification for using any safety factor less than 10X.

US EPA Memorandum, April 22, 2004 This is a memorandum from Vicki L. Dellarco, Health Effects Division, to Lois Rossi, Registration Division, both of the Office of Pesticide Programs, regarding the waiver justification for an inhalation developmental neurotoxicity study in rats, as required in the above citations. Dow submitted a waiver justification to the Agency in which the bases given were (as listed by the Agency):

- Essentially no chronic dietary exposure

- Minimal potential inhalation exposures or short duration (1-2 days)

- Animal welfare concerns (1500 to 4000 animals)

- Potentially confounded scientific and technical aspects of conducting an inhalation DNT study

Dow also mentioned that they had conducted a recent metabolism study in rats showing the rapid release of fluoride. Given the known toxicity of fluoride and the minimal exposure, neurotoxicity to adult or developmental neurotoxicity would be unlikely.

The staff at the Agency agreed with the arguments of Dow regarding minimal exposure potential and unlikelihood of neurotoxicity occurring due to dietary or inhalation exposure. The 10X uncertainty factor, was to be retained for the lack of a DNT study, in addition to the 10X for animal to humans and the 10X for variations in sensitivity among humans (1000X total). This composite safety factor would provide "ample" protection.

DPR comments in reference to the 4 bases of Dow listed by the Agency

The comment about essentially no chronic dietary exposure seems appropriate, based on desorption of sulfur fluoride with time. Residue data would confirm dietary estimates.

Duration of exposures of 1-2 days seems questionable for "bystanders" near food use fumigation chambers (as opposed to fumigated structures). With multiple uses of a given chamber, the bystander exposure could be repeated with some frequency.

The number of animals needed (4000) seems excessive. It is assumed that the number, 1500, includes the pups as well as the pregnant dams with sufficient dams per dose group to produce 20 litters with the appropriate numbers of pups per sex. Where 4000 might become involved is unclear. Although DPR is in accord with the efforts to minimize the number of animals used in toxicity testing, the primary responsibility to toward the assessment of health risks to the people of California.

Regarding the last basis, potentially confounded scientific and technical aspects of an inhalation DNT study, a 2-generation reproduction study was conducted by Dow using the inhalation route. A DNT study and a reproduction study should present similar technical

situations. In the reproduction study, males and females were exposed to 0, 5, 20 or 150 ppm for 6 hours per day. Females (as in a DNT study) were exposed every day during gestation until GD 20 and not exposed until day 5 of lactation. From days 5 - 21 postpartum, pups were separated from the dams while they were exposed to sulfuryl fluoride for 6 hours per day, according to the report. The pups remained in the nesting cages. In that study, no treatment-related effects on pup weights were noted except at the high dose, possibly secondary to decreased maternal body weight. It should be possible to examine pups for DNT parameters during this period of exposure of the dams. It is unclear how the separation of pups from dams for a DNT study differs from the separation for the reproductive toxicity study. The examination of pups for neurotoxic endpoints, such as motor activity, is part of any DNT study, and not specific to an inhalation DNT study. Therefore, the basis of "technical aspects" given by Dow is not adequate alone, since similar technical aspects would have been present in the reproductive toxicity study.

Although not part of the list of bases from DOW in the memorandum of US EPA are the results of a metabolism study in male rats (ID 001155, May 22, 2002) which indicated that sulfuryl fluoride is rapidly absorbed and rapidly converted to fluoride, fluorosulfate and sulfate. Therefore, the metabolism study suggests that no sulfuryl fluoride *per se* should be detectable in blood or urine, for example. The implication is that a DNT study would, in practicality, test fluoride [as should be true of the other studies conducted for toxic effects].

Although the Department would prefer to have actual data from a DNT study to evaluate whether there is any specific sensitivity of the fetus and/or newborn to inhalation of sulfuryl fluoride, the continued use of a 10X uncertainty factor (1000X total) should provide protection of those populations. Therefore, the Department agrees with the waiver given by US EPA to the conduct of a DNT study with sulfuryl fluoride at this time.